Clinical review

Regular Review

Ectopic pregnancy

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Ectopic pregnancy (fig 1) causes major maternal morbidity and mortality, with pregnancy loss, and its incidence is increasing worldwide.[1–3] In northern Europe between 1976 and 1993 the incidence increased from 11.2 to 18.8 per 1000 pregnancies,[2] and in 1989 in the United States admissions to hospital for ectopic pregnancy increased from 17 800 in 1970 to 88 400.[4] These changes were greatest in women over 35 years of age.[2 4] In the United Kingdom there are around 11 000 cases of ectopic pregnancy per year (incidence 11.5 per 1000 pregnancies), with four deaths (a rate of 0.4 per 1000 ectopic pregnancies).[1]

Summary points

- The incidence of ectopic pregnancy is increasing, mainly due to the increased incidence of pelvic inflammatory disease caused by *Chlamydia trachomatis*
- Ectopic pregnancy must be excluded in a sexually active woman with a positive pregnancy test, abdominal pain, and vaginal bleeding
- Early ultrasonography should be available in subsequent pregnancies for women who have had an ectopic pregnancy
- Diagnosis cannot be made clinically or in the community
- Treatment should be tailored to individual needs; in selected cases medical management can be as effective as laparoscopic salpingostomy
- Conservative surgery results in slightly higher rates of intrauterine pregnancy and higher recurrent ectopic pregnancies

Methods

We review the incidence, causes, diagnosis, and management of ectopic pregnancy. The evidence presented is from a combination of selected published papers identified from Medline and a reflection of clinical practice in our unit. Medline was searched with the term "ectopic pregnancy" and combined with terms such as incidence, risk factors, methotrexate, salpingectomy, salpingostomy, etc.

Risk factors

Although a proportion of women with ectopic pregnancy have no identifiable causal factors, the risk is increased by several factors: previous ectopic pregnancy,[5] tubal damage from infection or surgery,[6] a history of infertility,[6] treatment for in vitro fertilisation,[7] increased age,[2 4] and smoking.[8]

A history of pelvic inflammatory disease is particularly important[6 9] and has been implicated in the increased incidence of ectopic pregnancy.[9 10] After acute salpingitis, the risk of an ectopic pregnancy is increased sevenfold.[9] This is particularly true of *Chlamydia trachomatis*, the main cause of pelvic inflammatory disease in the United Kingdom.[11] Comprehensive programmes to prevent chlamydia not only decrease the incidence of *C trachomatis* infections but also the rate of ectopic pregnancies.[12 13]

Previous female sterilisation[14] and current use of an intrauterine contraceptive device[15] are only risk factors when patients with ectopic pregnancy are compared with pregnant controls and not with non-pregnant women. This is because overall the risk of pregnancy in these situations is low, but if pregnancy does occur an ectopic pregnancy is more likely. The risk of ectopic pregnancy after sterilisation is only 7.3 per 1000 within 10 years.[14]

The incidence of ectopic pregnancy after assisted reproductive techniques is 4%,[7] which is 2-3 times greater than the background incidence. The main risk factor in this group is tubal infertility. The incidence of heterotopic pregnancy (an ectopic pregnancy together

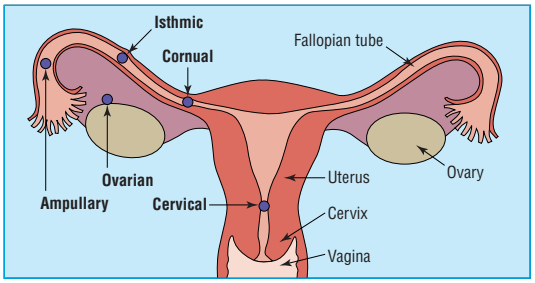

Fig 1 Sites of ectopic pregnancies

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Percentage occurrence of history and presenting signs with ectopic pregnancy

Abdominal pain (97%)
Vaginal bleeding (79%)
Abdominal tenderness (91%)
Adnexal tenderness (54%)
History of infertility (15%)
Use of an intrauterine contraceptive device (14%)
Previous ectopic pregnancy (11%)

with an intrauterine pregnancy) is also increased after assisted reproductive techniques.

Presentation

Ectopic pregnancies usually present after seven (SD two) weeks of amenorrhoea. The diagnosis can be difficult unless the condition is suspected and can be confused with miscarriage, an ovarian accident, or pelvic inflammatory disease (see box). The abdominal pain is usually lateral. However, history and physical examination alone do not reliably diagnose or exclude ectopic pregnancy, as up to 9% of women report no pain and 36% lack adnexal tenderness. The presence of known risk factors can increase suspicion, but any sexually active woman presenting with abdominal pain and vaginal bleeding after an interval of amenorrhoea has an ectopic pregnancy until proved otherwise. Women who present in a collapsed state usually have had prodromal symptoms that have been overlooked. Tubal rupture is rarely sudden since it is due to invasion by the trophoblast (fig 2). Therefore, if there is any suspicion, hospital referral for investigation is mandatory.

Hospital diagnosis

Referral should preferably be to a unit dedicated to managing problems early in pregnancy as this allows ease of investigations and continuity of outpatient care. The initial investigations are a sensitive pregnancy test and ultrasonography. The presence of an intrauterine pregnancy generally excludes ectopic pregnancy, although other ultrasound findings have to be considered, especially if symptoms are atypical, severe, or persistent. The use of quantitative measurement of serum concentrations of β human chorionic gonadotrophin together with transvaginal ultrasonography has improved the diagnosis.[16] There is, however, controversy about the concentration of serum human chorionic gonadotrophin that is diagnostic.[17 18] In the presence of an ectopic mass or fluid in the pouch of Douglas, a cut off point for a serum concentration of human chorionic gonadotrophin of 1500 IU/l is recommended, but in the absence of any ultrasound signs the higher concentration of 2000 IU/l should be the cut off point before an ectopic pregnancy is diagnosed.[18] Ectopic pregnancies produce lower concentrations of human chorionic gonadotrophin than normal pregnancies, but the change in concentrations provides more information.[19 20] In a normal pregnancy, serum concentrations of human chorionic gonadotrophin double every 2-3.5 days in the fourth to eighth week of gestation reaching a peak around the eighth to 12th week, as calculated from the last menstrual period (fig 3).[20 21] A failure of this increase is suggestive of an ectopic pregnancy although it is also associated with early pregnancy failure. A two day sampling interval has been recommended if paired serum samples are being tested.[19] The accurate diagnosis of ectopic pregnancy can be life saving, reduce invasive investigations, and allow conservative treatment.

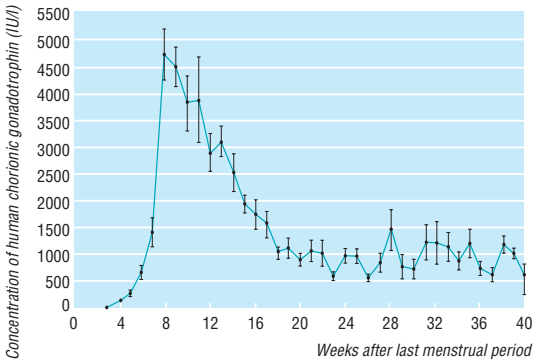

Fig 3 Mean (SE) serum concentrations of human chorionic gonadotrophin in normal pregnancy (adapted from Braunstein et al 1996[21])

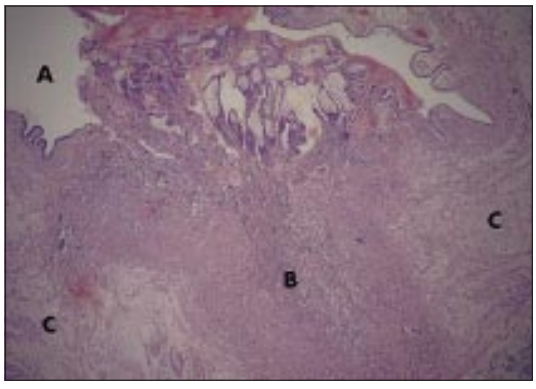

Fig 2 Trophoblast invading wall of fallopian tube (×25). A, tubal lumen; B, trophoblast; C, tubal wall

Treatment

Expectant and medical management are possible, and should be considered in selected cases, but they are not widely practised in the United Kingdom. Surgery remains the mainstay of treatment, possibly overtreating a number of cases.

Expectant

Some ectopic pregnancies resolve spontaneously, and expectant management is possible in selected cases. This is not related to the size of the ectopic pregnancy on an ultrasonogram[22 23] but the initial serum titre of human chorionic gonadotrophin, and the trend in titres are independent predictors of success.[24] It is important, therefore, to serially monitor serum titres of human chorionic gonadotrophin in patients who are being managed expectantly. The higher the serum concentration the more likely expectant management will fail.[22 24] Overall, if the initial serum concentration of human chorionic gonadotrophin is less than 1000

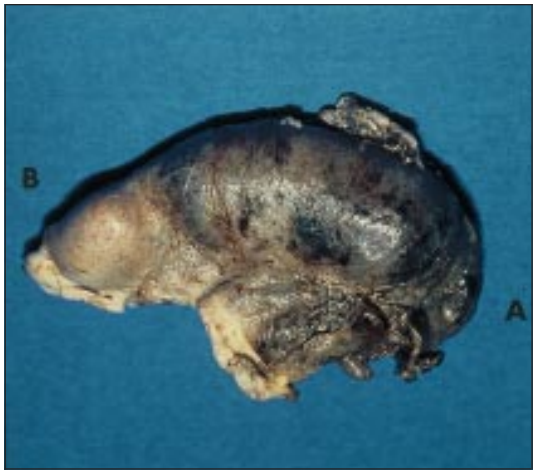

Fig 4 Unruptured tube with ectopic pregnancy. A, fimbrial end; B, cornual end

IU/l, expectant management is successful in up to 88% of patients.[24]

Medical

Methotrexate, a folic acid antagonist, is used for medical management in patients before rupture who are haemodynamically stable (fig 4).[25] It can be given intramuscularly or injected into the ectopic pregnancy, a route that delivers high concentrations locally with smaller systemic distribution. However, rates of successful treatment are lower than with systemic methotrexate, and it requires a laparoscopic or ultrasound guided needle procedure. Methotrexate in a single dose is more convenient than the variable dose regimen but may carry a higher risk of persistent ectopic pregnancy.[5] Close follow up with serial measurements of serum concentrations of human chorionic gonadotrophin is required. A second course of treatment may be necessary, and some patients may require surgical intervention. Methotrexate treatment may produce significant side effects.

Surgical

Surgical treatments may be radical (salpingectomy) or conservative (usually salpingostomy), and they may be performed by laparoscopy or laparotomy. Salpingectomy is the treatment of choice if the fallopian tube is extensively diseased or damaged as there is a high risk of recurrent ectopic pregnancy in that tube.

Generally, hospital stay (1.3 days) and convalescence (2.4 weeks) are shorter after laparoscopy than with laparotomy (3.1 days and 4.6 weeks respectively).[26 27] Both techniques produce similar rates of complications[27] and persistent trophoblast.[28] If there is a risk of persistent trophoblast, follow up with serial measurements of serum concentrations of human chorionic gonadotrophin is necessary. Since no single postoperative concentration of human chorionic gonadotrophin is predictive, follow up until complete resolution is necessary.[25] The need for a second laparoscopy should be based on symptoms rather than changes in concentrations of human chorionic gonadotrophin.[26–28] In a randomised controlled trial, methotrexate and laparoscopic salpingostomy were equally effective.[29]

Cost of treatment

The cost of salpingostomy is slightly more than salpingectomy in the short term.[30] Both treatments are equally effective initially, but additional treatment for persistent ectopic pregnancies is occasionally required after salpingostomy. Although it is comparatively simple to cost the acute episode, calculating the long term costs of subsequent infertility treatment and treatment for recurrent ectopic pregnancy is more difficult.

The psychological cost is often overlooked as it is not generally viewed in the same way as other pregnancy loss. It would seem that the women have similar grief reactions to those with miscarriages but have the additional trauma of the potential reduction in fertility. Support networks such as the Miscarriage Association are recommended to women after miscarriage but, until recently, there has been no specific support group for woman after ectopic pregnancy. The recently formed Ectopic Pregnancy Trust evolved out of this need and provides both information and support.

Fertility after treatment

Rates of intrauterine pregnancy after expectant management are comparable to those achieved after medical or surgical management, varying between 80% and 88%,[31 32] and rates for recurrent ectopic pregnancy vary between 4.2% and 5%.

A population based cohort study reported a pregnancy rate of 66% regardless of whether treatment was surgical or medical.[33] Of those who conceived, 90% achieved an intrauterine pregnancy and 10% had recurrent ectopic pregnancy. The risk factors for recurrent ectopic pregnancy are previous spontaneous miscarriage, tubal damage, and age greater than 30.[25] After methotrexate, between 62% and 70% of women had a subsequent intrauterine pregnancy and around 8% had recurrent ectopic pregnancy.[23 25]

When comparing conservative and radical surgery, the results are conflicting, with pregnancy rates varying from no significant difference[34] to lower rates of both intrauterine pregnancy and recurrent ectopic pregnancy after salpingectomy.[23 35 36]

Irrespective of type of tubal surgery, laparoscopic treatment resulted in a higher rate of intrauterine pregnancy (77% versus 66%)[35] and a lower rate of recurrent ectopic pregnancy (7% versus 17%)[27] compared with laparotomy. A history of infertility is, however, an important factor, with an overall conception rate of 77% for all methods of surgical treatment and a rate of recurrent ectopic pregnancy of around 10%.

Despite tubal preservation in around 90% of patients and patency in 55%-59%, neither systemic treatment with methotrexate nor laparoscopic salpingostomy improved subsequent pregnancy performance.[29] Treatment should therefore be directed at therapeutic need and the wishes of the patient.

Conclusion

Since ectopic pregnancy cannot be diagnosed in the community, all sexually active women with a history of lower abdominal pain and vaginal bleeding should

be referred to hospital early for ultrasonography and, if necessary, measurement of serum concentrations of human chorionic gonadotrophin. Women with a history of ectopic pregnancy should have early access to ultrasonography to verify a viable intrauterine pregnancy in their subsequent pregnancies. Diagnostic laparoscopy is necessary if the clinical situation cannot be clarified or if the patient's condition deteriorates.

Expectant and medical management of ectopic pregnancy are effective options in selected cases as long as adequate facilities for monitoring are available. If surgery is necessary, the laparoscopic route results in shorter hospital stay, but there is no clear advantage of salpingostomy over salpingectomy. The decision should therefore be made on an individual basis. Methotrexate and laparoscopic salpingostomy are equally successful in treating ectopic pregnancy.[36] Ectopic pregnancy can be prevented by decreasing the incidence of pelvic inflammatory disease and *C trachomatis* infections and improving their treatment.

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